REMARKS

In response to the Final Office Action mailed February 22, 2007, the listing of canceled claims has been corrected. Claims 55-77 are pending and under consideration. Reconsideration of the subject application is respectfully requested in view of the following remarks.

Rejections under 35 U.S.C. § 112 (enablement)

Claims 55-77 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner contends that the specification is not enabling for methods of generating a blood vessel in a mammal by administering bone marrow stromal cells to the mammal. In particular, the Examiner relies on several post-filing references to support his assertion that it would require undue experimentation to demonstrate that systemic or intraperitoneal administration of stromal cells would result in the proper differentiation and generation of blood vessels at the site where said blood vessels are required and not at undesired sites, for the claimed methods.

Applicants respectfully traverse the rejection on the following grounds.

The thrust of the Examiner's assertions appears to be that the specification does not enable the use of the claimed methods due to a lack of evidence regarding their human implementation. If this is true, the Examiner is asserting that the claimed invention lacks *in vivo* utility. Although this rejection is not made under 35 U.S.C. § 101, the legal standard to be applied is the same. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (Although the Examiner rejected the methods based on § 112, a § 101 rejection for lack of utility would also have been proper.) (See also "Legal Analysis Supporting Utility Examination Guidelines 60 F.R. 36263, July 14, 1995.)

Applicants respectfully submit that this rejection is improper in view of the PTO Guidelines. In *no* case has a Federal court required an applicant to support an asserted utility with data from human clinical trials. Moreover, in *In re Brana*, the Federal Circuit emphatically rejected the PTO position that human clinical testing is necessary to establish practical utility for an antitumor agent. 51 F.3d 1560. Importantly, the court noted, citing *In re Krimmel*, 130 U.S.P.Q. 205 (C.C.P.A. 1961):

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, **even though it may eventually appear that the compound is without value in the treatment of humans**. (Emphasis added)

As noted in Applicants' previous reply, Applicants enjoy a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112, unless there is a reason to doubt the objective truth of the specification. See, *In re Marzocchi*, 439 F.2s 220, 169 USPQ367 (CCPA1971). The initial burden of establishing a basis for denying patentability to a claimed invention rests upon the examiner. Applicants respectfully submit that this burden has not been met.

The Examiner cites numerous post-filing date references to support the position that the claimed invention is not enabled. Citing *In re Wright*, the Examiner asserts that "if individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered." However, the Examiner has selectively reviewed only those sections of the cited references that discuss potential pitfalls of the technology, while completely ignoring the central findings of the references, which clearly show that the invention is feasible. Thus, regardless of whether or not a later dated publication can supplement an insufficient disclosure, it is wholly unfair to focus solely upon the technical hurdles faced by those in the field while completely ignoring the successes.

For example, Nagaya *et al.*, in fact, demonstrate that "intravenously administered MSCs were capable of engraftment in the ischemic myocardium and that the engrafted MSCs differentiated into cardiomyocytes and vascular endothelial cells, resulting in myogenesis and

angiogenesis." (first paragraph of discussion, page H2673). Nagaya *et al.* further show that MSC transplantation decreases myocardial infarct size and improves cardiac function. Nagaya *et al.* go on to say that "MSC implantation has been shown to induce therapeutic angiogenesis in a rat model of chronic hindlimb ischemia" (*see*, Al-Khaldi *et al.*, Ann Thorac Surg 75:204-209, 2003). The authors suggest that "these findings support the theory that intravenously administered MSCs are able to differentiate into vascular endothelial cells in the ishcemic myocardium." All of these observations have been ignored by the Examiner in favor of certain statements made by the authors that the Examiner asserts demonstrate the potential detrimental aspects of the invention.

Specifically, the Examiner asserts that Applicants have not addressed the issue of Nagaya's observation that only a small percentage of transplanted MSCs were incorporated into the heart, opining that this observation is an important consideration in the use of MSCs in any treatment method as it highlights the difficulty of delivery of MSCs to a particular target site. On the contrary, Applicants submit that the actual number of cells that were incorporated into the heart does not negate the central finding of the paper which is that administration of MSCs improves cardiac function. The fact that this improvement requires only a small percentage of MSCs in the heart in fact further supports the important therapeutic value of these transplanted cells for generating blood vessels *in vivo*.

Regarding Zisch, Applicants reiterate that the EPCs described therein are not equivalent to the currently recited bone marrow stromal cells, and that it is inappropriate for the Examiner to rely on this reference. In particular, Applicants note that Zisch reports that EPCs are CD34+ cells, *i.e.*, hematopoietic cells. The currently recited BMSCs are stromal cells, defined in the specification as MSCs or adherent cells, and, therefore, are CD34-. Applicants further submit that Zisch provides no suggestion that one should use such BMSCs to create new blood vessels. In addition, although Zisch reports that two references discuss CD34- populations that contain EPC activity (ref 16 and 20), these references deal respectively with umbilical cord blood and a monocyte-enriched population that also expresses dendritic cell antigens. Accordingly, these cells are clearly distinguishable from the presently recited bone marrow

stromal cells, and conclusions based upon this reference cannot be directly applied to the presently claimed methods.

Nonetheless, even assuming *arguendo* that these cells were equivalent, once again, the Examiner has ignored the central findings of the paper, while focusing only on the potential hurdles mentioned by the authors in their conclusory statements. In particular, the Examiner cites a passage from the "Conclusions" section of the paper that notes that improvement in perfusion of recipient tissue is unlikely to result from cell replacement alone, but instead stems from the provision by EPCs of paracrine growth factor/cytokine signals. The Examiner further quotes the author's statement that "The interaction between the host environment and EPCs has not been well established...the surprising plasticity of primary EPCs to change fate into cardiomyocyte or mesenchymal phenotypes warrants further investigation". Applicants respectfully submit that this statement is taken out of context and further note that the statement continues on by saying "warrants further investigation so that their potential for exploitation in cardiovascular tissue engineering applications can be ***further appreciated***." Again, that primary EPCs may change into mesenchymal phenotypes does not negate the observations of the author indicating the feasibility of the invention. As one example, Zisch states at page 425, second column:

> The benefits of re-transplanting autologous EPCs for increasing tissue reperfusion have been established in multiple studies of experimentally induced acute or chronic ischemia of heart or limbs as well as for *in situ* re-endothelialization of denuded arteries to inhibit thrombus formation or neointima hyperplasia. Preclinical work showed that infusion or injection of adult EPCs after acute myocardial infarction resulted in profound and sustained improvement of cardiac function. ... Early data obtained in clinical pilot trials of acute myocardial infarction, advanced coronary artery disease or leg ischemia suggest that cell-based reperfusion therapy is both safe and feasible and capable of achieving revascularization. (emphasis added)

Moreover, the Examiner's statement in the first Office Action at page 8 that "following implantation [at numerous sites in a mammal], the MSCs, would likely alter the

physiological state of the mammal by providing paracrine growth factor/cytokine signals" is complete conjecture with no evidence provided to support such a statement.

With respect to Dzau *et al.*, this reference is also directed to EPCs, so the above comments regarding the applicability of this reference apply. However, this reference also has been taken out of context by the Examiner and viewed only in a negative light, while the positive potential of the EPCs is ignored. In particular, the Examiner has cited a paragraph from the section entitled "Potential Problems with Therapeutic Use of EPCs" regarding the impaired function of EPCs in certain populations and the importance of purity and developmental state of the cells. Applicants note that the impaired function of EPCs in certain patient populations (*e.g.*, diabetic patients) does not preclude enablement of the invention. In other words, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). Further, Applicants note that this quoted section from Dzau *et al.* is referring to the impairment of the patient's own EPCs as potentially underlying some of the vascular complications associated with, *e.g.* diabetes or aging. As such, Applicants submit that impairment of the EPCs in these patients would apply more particularly to autologous transplantation and not allogeneic transplantation. Thus, transplantation of EPCs from a disease free source would actually benefit these patient populations. In fact, this point is highlighted by Dzau *et al.* at page 10, first column: "In this regard, Schatteman *et al.* showed that transplantion of CD34+-derived angioblasts from non-diabetic mice markedly accelerates blood flow restoration in ischemic hind limb of diabetic mice in association with enhanced neovascularization."

Finally, with regard to the observations of Yoon *et al.* referred to by Dzau *et al.* in the paragraph quoted by the Examiner, a closer review of the data described in Yoon *et al.* reveals that only injection of total bone marrow cells led to calcification of the heart. No echogenic areas were observed in rats receiving bone marrow stem cells or PBS (see page 3155,

section entitled Echocardiography). Further, Applicants note that the cells were injected directly into the hearts of rats, and, therefore, the results are likely not relevant to the systemic administration of bone marrow stromal cells of the present invention. Moreover, Yoon *et al.* stress in the abstract and the introduction of the paper that "Thus far, no significant deleterious effects or complications have been reported in any preclinical or clinical trials using BM-derived cells for treatment of various cardiac diseases."

Thus, Applicants submit that the Examiner has not satisfied the initial burden to establish a reasonable basis to question enablement, since all of the references cited by the Examiner actually appear to demonstrate post-filing reduction to practice of the claimed invention, regardless of the Examiner's reliance solely on negative statements made therein and regardless of the fact that two of the three cited references do not relate to the claims MSCs. Accordingly, Applicants submit that the claims are enabled and respectfully request reconsideration of the claims and withdrawal of the rejection.

Provisional Rejection under Obviousness-type Double Patenting

Claims 55-77 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 55-70 of co-pending Application No. 10/423,232 and over claims 17-28 of co-pending Application No. 10/844,235.

Applicants respectfully traverse this ground for rejection and submit that neither of these references teach or suggest in the claims a method for generating a blood vessel in a mammal. In particular, the claims in co-pending Application No. 10/423,232 are directed to a process for generating heart tissue and the claims in co-pending Application No. 10/844,235 are directed to a method of treating a mammal having undergone marrow ablation. As such Applicants submit that the present claims are not obvious in view of the cited applications. Nevertheless, as term of the present patent will not be affected and without acquiescing to the ground of rejection, Applicants will consider submitting a terminal disclaimer once the claims are determined to be allowable.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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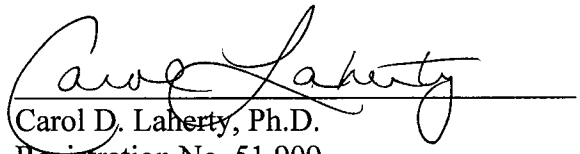

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